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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,619	11/15/2001	Eugene D. Thorsett	002010-596	7434

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 04/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,619	THORSETT ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 35-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,35-45 and 57* is/are allowed.

6)☒ Claim(s) *46-56,58 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election of Group I is acknowledged, as is the elected specie.

Claims 1 and 35-59 remain pending.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-56, 58, 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification states (p. 334, line 29+) that each of the compounds of examples 1-373 exhibited an IC_{50} of 15 μM or less in an assay which endeavors to assess the binding of compounds to $\alpha 4\beta 1$ integrin. From this, applicants are asserting that the compounds will be effective in the treatment of Alzheimer's disease, AIDS dementia, encephalitis, MS, tissue transplantation, meningitis, and tumor metastasis. However, applicants have provided no evidence that this is the case. While it may be true that $\alpha 4\beta 1$ integrins are peripherally involved in each of these disease states, it is far from clear that a disorder in the binding of integrins is the primary cause of the diseases. In

addition, it is not established that the compounds, if administered, will reach the appropriate anatomical site(s), that they will accumulate to a sufficient extent to be effective

The assertion by the examiner is that (a) structure/activity relationships in VLA-4 antagonism are unpredictable, and (b) treatment of inflammatory conditions is unpredictable as well. Consider the following:

- Dutta (*Journal of Peptide Science* **6**, 321-341, 2000) has examined the efficacy of various peptides in the antagonism of VLA-4/VCAM-1 binding. As stated on page 329, col 2, last two lines, the following two compounds were inactive both *in vitro* and *in vivo*:

  cyclo[Ile-Leu-Asp-Val-NH $(CH2)_2CO$]
  Ac-cyclo(Orn-Leu-Asp-Val)

  These peptides are minor variations of peptides that were active.

- Arrhenius (*USP 5,688,913*) discloses (cols 17-18) several examples of compounds which failed to antagonize VLA-4. These compounds are minor variations of other compounds that were potent antagonists of VLA-4.

- Komoriya, Akira (*J. Biol. Chem.* **266** (23), 15075-15079, 1991) discloses that in an assay of $\alpha_4\beta_1$ activity, the pentapeptide EILEV was active, but pentapeptide EILDV was not. This latter peptide differs from the former by just one methylene unit.

- Haworth, Duncan (*Br. J. Pharmacol.* **126**(8), 1751-1760, 1999) discloses various VLA-4 antagonists. At least one of the disclosed compounds was inactive; this compound differed by only a few methylene units from a compound that was active.

- Haubner (*J. Am. Chem. Soc.* **118**, 7881, 1996) discloses (table 2) two compounds which failed to inhibit fibrinogen binding to the $\alpha_{IIb}\beta_1$ receptor, and vitronectin binding to the the $\alpha_V\beta_3$ receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity. These data argue for "unpredictability" in structure activity relationships of integrins generally. In addition, the "unpredictability" in structure activity relationships of

RGD-peptides has direct relevance to the claimed compounds. As disclosed in Yang Y (*European Journal of Immunology* **28** (3) 995-1004, 1998) RGD-containing peptides can bind to VLA-4. Thus, if one cannot predict structure activity relationships of RGD peptides in their binding to VLA-4, it stands to reason that such unpredictability extends to other compounds which either do bind VLA-4, or which are asserted to exhibit such an effect.

In addition to the foregoing, the following references teach "failure" in the treatment of one or more inflammatory conditions:

Vatistas N J, "Infection of the intertubercular bursa in horses: four cases (1978-1991)", [*Journal of the American Veterinary Medical Association* **208** (9) 1434-7, 1996];

Tait A, "Synthesis and antiinflammatory activity of 2,6-bis(1,1- dimethylethyl) phenol derivatives" (*Farmaco* **48** (10) 1463-73, 1993);

Kurokawa M "Synthesis and antiinflammatory activity of cis- and trans- 6,6a, 7,8,9,10,10a,11- octahydro-11-oxodibenzo[b,e]thiepinacetic and -oxepinacetic acids" (*Journal of Medicinal Chemistry* **33** (2) 504-9, 1990);

Uren M F, "The effect of anti-inflammatory agents on the clinical expression of bovine ephemeral fever" (*Veterinary Microbiology* **19** (2) 99-111, 1989;

Crossley M J, "Studies on the effects of pharmacological agents on antigen-induced arthritis in BALB/c mice" (*Drugs Under Experimental and Clinical Research* **13** (5) 273-7, 1987).

Thus, structure/activity relationships involving VLA-4 are unpredictable. Perhaps it is true that many of the claimed compounds will exhibit an IC_{50} of 15 *micro*molar in an assay of VLA-4. However, the significance of this number (15 μM) with respect to treatment of treatment of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple

sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia is unknown. No correlation has been established between this "15 μM" parameter, and successful treatment of any of the foregoing diseases. Moreover, other issues such as bioavailability and pharmacokinetics are not reflected in this "15 μM" number.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As is evident, extrapolation from an observation of VLA-4 binding in vitro to treatment of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia will produce "unpredictable" results.

In addition to the foregoing, consider the following:

- Pierce, J. W., ("Salicylates inhibit I kappa B-alpha phosphorylation, endothelial-leukocyte adhesion molecule expression, and neutrophil transmigration", Journal of Immunology, 156 (10) 3961-9, 1996) discloses that aspirin inhibits ICAM-1 and VCAM-1 expression. In a similar vein, Gonzalez-Alvaro I ("Interference of nonsteroidal antiinflammatory drugs with very late activation antigen 4/vascular cells adhesion molecule 1-mediated

lymphocyte-endothelial cell adhesion", Arthritis and Rheumatism 41 (9) 1677-88, 1998) discloses that indomethacin inhibits VLA-4/VCAM-1 interactions. If applicants' assertions were correct, the skilled artisan would predict that success in the treatment of inflammatory conditions would be achieved by any compound which antagonizes VLA-4/VCAM-1 interactions. Yet this is not what one finds. For example, Goldenberg M M ("A pharmacologic analysis of the action of platelet-activating factor in the induction of hindpaw edema in the rat", Prostaglandins 28 (2) 271-8, 1984) discloses that neither indomethacin nor aspirin was effective to inhibit an inflammatory response to paw edema in rats. Similarly, Zuany-Amorim C. (European Journal of Pharmacology 257 (3) 211-6, 1994), discloses that aspirin failed to inhibit inflammatory responses to antigen (e.g., page 214, col 1). These findings of Goldenberg and of Zuany-Amorim support the examiner's contention that one cannot predict success in the treatment of inflammatory diseases merely because one can antagonize VLA-4/VCAM-1 interactions in vitro. As two more examples, Rordorf C "Arthritis in MRL/LPR mice and in collagen II sensitized DBA-1 mice and their use in pharmacology", International Journal of Tissue Reactions 9 (4) 341-7, 1987 discloses that indomethacin was not effective to treat arthritis in an animal model, and Goldlust M B (Agents and Actions 11 (6-7) 729-35, 1981) discloses that aspirin was not effective to treat synovitis in rabbits.

- Theien, B. E. (*Journal of Clinical Investigation* **107** (8) 995-1006, 2001) compared the ability of anti-VLA-4 to regulate proteolipid protein (PLP) 139-151-induced R-EAE when administered either before or after disease onset. Preclinical administration of anti-VLA-4 either to naive recipients of primed encephalitogenic T cells or to mice 1 week after peptide priming, i.e., before clinical disease onset, inhibited the onset and severity of clinical disease. In contrast, Ab treatment either at the peak of acute disease or during remission exacerbated disease relapses and increased the accumulation of CD4(+) T cells in the CNS. Most significantly, anti-VLA-4 treatment either before or during ongoing R-EAE enhanced Th1 responses to both the priming peptide and endogenous myelin epitopes released secondary to acute tissue damage. Collectively, these results suggest that treatment with anti-VLA-4 Ab may be problematic in treating established autoimmune diseases such as MS. Accordingly, one cannot predict success in the treatment of MS based on the propensity of a compound to antagonize VLA-4.

- Saez-Torres I ("Peptide T does not ameliorate experimental autoimmune encephalomyelitis (EAE) in Lewis rats", *Clinical and Experimental Immunology* **121** (1) 151-6, 2000) discloses that it is known in the art that peptide T inhibits T cell activation and cytokine production and function. Saez-Torres studied the ability of peptide T to ameliorate EAE in Lewis rats. Peptide T was administered subcutaneously at different doses and phases of the disease according to several treatment protocols. The authors concluded that peptide T neither prevents nor ameliorates EAE in Lewis rats. This supports the conclusion that one cannot "predict" success in the treatment of inflammatory conditions, even if one is able to inhibit T cell activation and cytokine production. This finding of Saez-Torres is relevant in part because VLA-4 is prominently expressed on circulating T-cells.

The foregoing teachings further support the conclusion that one cannot predict efficacy in the treatment of human disease merely by modulating *alpha* 4/ligand interactions *in vitro*. Clearly, "undue experimentation" would be required to practice the claimed invention. It is suggested that claims 58 and 59 be cancelled, and that the terms "pharmaceutical" and "therapeutically effective" be deleted from the claims.

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- The patents that applicants have listed on the IDS have been stricken therefrom and listed instead on a PTO-892 form. [Examiners are required to list the class/subclass of each patent].

- The provisional applications (e.g., S.N. 60/022890) and the US application (08/821825) should not be listed on the "US Patent Documents" section of the IDS. They should be listed in a section entitled "Other Documents" (or an equivalent expression). [This is a matter that is not at the discretion of the examiner]. It is suggested that applicants re-submit an IDS with these applications listed in the appropriate section.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600